

REMARKS

Claims 150-282 are presented for prosecution on the merits in this continuation application filed under Rule 1.60.

Changes to the specifications have also been effected in several instances as follows. **First**, a more descriptive title has been substituted and an updated section cross-referencing this application with other prior related applications has been added on page 1 in the specification. **Second**, the amendments in Applicants' May 31, 1994 Amendment Under 37 C.F.R. §1.116 have been made to six (6) pages (2, 3, 21, 44, 50 and 51). In the May 19, 1995 Office Action issued in the immediate parent continuation application (Serial No. 08/342,667, filed on November 21, 1994), the Examiner had indicated that these amendments, which consisted largely of misspelling or citation corrections, had not been entered. Accordingly, those amendments have now been implemented, and their entry requested.

Third, as was noted by the Examiner in the January 10, 1995 Office Action issued in a related sister application (Serial No. 08/032,769, filed on March 16, 1993), the word "Fungi" (page 12, line 2) was misspelled, and this has now been corrected. **Fourth**, based upon a review of the entire prosecution, other misspellings or clarifications have been made on pages 52, 54 and 56. Finally, the citations for various patents and applications cited on pages 20 and 21 have been updated. These updated citations will be helpful to future readers and examiners, who in attempting to understand the present invention, will be able to resort, as necessary or appropriate, to granted U.S. patents referenced in the specification. It is respectfully submitted that none of the foregoing amendments to the specification constitutes the insertion of new matter. Their entry is respectfully urged.

For purposes of streamlining examination, Applicants are also pursuing in this case the subject matter of the related sister application mentioned above, Serial No. 08/032,769, which is directed to method and kit claims represented by claims 261-282 above. Most if not all of the issues affecting the composition claims are similar and even identical to those affecting the method and kit claims. Such

issues include indefiniteness under 35 U.S.C. §112, second paragraph, and obviousness under 35 U.S.C. §103.

Changes to the composition claims have taken a number of forms. **First**, the claims are directed to compositions comprising a signal generating portion capable of providing a detectable signal (independent claims 150, 201, 202, 253, 255, and 257). **Second**, neither the term "universal" nor "non-radioactive" which had been presented in various prior claims is recited in the instant independent claims. The issue of the latter as a feature of the instant invention is discussed below in connection with the obviousness rejection (35 U.S.C. §103). **Third**, the expression "providing, directly or indirectly" has been altogether deleted from the new independent claims. As in the previous pending composition claims, the specific terms "directly" and "indirectly" continue to be taken up in separate dependent claims. See, for example, claims 191-194 and 243-246 (for instances of "direct" recitation) and claims 195-198 and 247-250 (for instances of "indirect" recitation).

Fourth, the phrase "or a variant thereof" which follows the Markush member, an M13 phage, has been amended to recite "or an M13 phage variant thereof." The last-mentioned amendment affects claims 176, 186, 228 and 238. It should be pointed out that the previous phrase was cited by the Examiner in separate indefiniteness rejections (35 U.S.C. §112, second paragraph) set forth in the above-referred May 19, 1995 and January 10, 1995 Office Actions. It should be pointed out that the modifying phrase, "or a variant thereof," was present in the originally filed claims, more specifically in the dependent claims setting forth the M13 phage as an embodiment. See original claims 32, 80, 87, 127 and 136. Thus, it is clear that the "variant" term modifies the M13 phage, and not some other Markush member. The new phrase is believed to be more definite in that it describes the variant as being of an M13 phage. Moreover, the skilled artisan would readily appreciate the meaning of the term "variant" as it applies to the M13 phage. **Fifth**, the phrase "a nucleic acid sequence of low complexity" has been changed to recite "a nucleic acid sequence of repeating low complexity." Again, it is believed that the foregoing change, which affects claims 177-178, 189-190, 229-230 and 241-242, renders the language more definite by indicating to the skilled artisan that "low" refers to the repeating nature of the nucleic acid sequence.

Changes to the "sister" method and kit claims referenced in the preceding paragraph have also been effected prior to their requested entry in the new claims above. The numbering of certain dependent claims has been changed to reflect a more logical order. Other changes to the method and kit claims follow those in the composition claims described above, and including the following:

- the deletion or absence of "universal" and "non-radioactive" language
- the deletion of the "direct" and "indirect" language in the generic claims
- the "variant" language being applied to the M13 phage Markush member
- the modification in various dependent claims of molecular bridging entity second portion and the signalling entity nucleic acid portion as comprising "a nucleic acid sequence of repeating low complexity."

In order to facilitate review of new claims 150-282, Applicants' attorney has set forth below the correspondence of each new claim against the previous claims in the predecessor application (Serial No. 08/342,667) or the related sister application (Serial No. 08/032,769).

<u>New Claim No.</u>	<u>Prior Related Claim</u>	<u>Changes in New Claim/Comments</u>
<u>COMPOSITION</u>		
<u>SERIAL NO 08/342.667</u>		
150	194	no "universal" or "non-radioactive" recitation deletion of "providing, directly or indirectly"
151	195	
152	196	
153	197	
154	198	

<u>New Claim No.</u>	<u>Prior Related Claim</u>	<u>Changes in New Claim/Comments</u>
155	199	
156	200	
157	201	
158	202	
159	203	
160	204	
161	205	
162	206	
163	207	
164	208	
165	209	
166	210	
167	211	
168	212	
169	213	
170	214	
171	215	
172	216	
173	218	
174	217	
175	219	
176	220	"or an M13 phage variant" inserted for "or a variant thereof"
177	221	"sequence of repeating low complexity" inserted for "sequence of low complexity"
178	222	"sequence of repeating low complexity" inserted for "said sequence"
179	223	
180	226	
181	230	
182	227	

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<u>New Claims</u>	<u>Corresponding to Former Claims 150-282 (3/5/96 Prelim'y Amend't</u>	<u>Comments/Changes Support</u>
308	164	
309	165	
310	166	
311	167	
312	-	U.S. Patent No. 5,241,060 (Engelhardt et al.) cited in specification (page 21, first paragraph: Serial No. 391,440, filed on June 23, 1982)
313	168	
314	169	
315	170	Other changes follow claim 300 above
316	171	
317	172	
318	-	See claim 312 above
319	173	
320	174	
321	175	Other changes follow claim 315 above
322	176	
323	177	
324	178	
325	179	
326	-	See specification (page 23, first paragraph; & page 25, second full paragraph through page 26, first full paragraph)
327	180	
328	181	Other changes follow claims 321 and 315 above
329	182	
330	-	See claims 318 and 312 above
331	183	
332	184	
333	185	
334	186	
335	187	

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<u>New Claims</u>	<u>Corresponding to Former Claims 150-282 (3/5/96 Prelim'y Amend't</u>	<u>Comments/Changes Support</u>
336	188	
337	189	
338	190	
339	191	See claims 291-294 above with respect to chemically modified or artificially altered polynucleotides
340	192	
341	193	
342	194	
343	195	
344	196	
345	197	
346	198	
347	199	
348	256	Support for "greater than five" is in specification (page 16, first paragraph)
349	256	
350	254	Support is in specification (page 22, first paragraph)
351		<i>ibid</i>
352		<i>ibid</i>
353	258	Support for the two "greater than 1" recitation is in specification (page 16, first paragraph and page 22, first paragraph)
354	258	<i>ibid</i>
355		<i>ibid</i>
356	-	page 22, first paragraph
357	-	<i>ibid</i>
358	252	
359	252	
360	259	"or hybridizing with" inserted or MBE first portion; "nucleic sequences or segments" substituted for sequence in MBE second portion; "more than one" SE substituted for "a" SE; & "or hybridizing with" inserted for SE nucleic acid portion

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<u>New Claims</u>	<u>Corresponding to Former Claims 150-282 (3/5/96 Prelim'y Amend't</u>	<u>Comments/Changes Support</u>
361	259	Changes follow claim 360 above except for "one or more polynucleotides... chemically modified or artificially altered (see claims 291- 294 above)
362	260	
363	261	
364	262	
365	263	"process" substituted for "method"; & "detectable" deleted before "complex" in the forming step
366	264	
367	265	
368	266	
369	267	
370	268	
371	269	
372	270	
373	271	See specification (page 28; see especially Wahl et al., U.S. Patent No. 4,302,204) <i>ibid</i> <i>ibid</i>
374	272	
375	273	
376	-	
377	-	Same as claim 378 above Same as claim 363 above
378	-	
379	273	
380	-	
381	-	
382	262	
383	263	
384	264	
385	265	
386	266	
387	267	

388	268	
389	269	
390	270	
391	271	
392	272	
393	273	
394	-	Same as claim 376 above
395	-	Same as claim 377 above
396	-	Same as claim 378 above
397	273	Same as claim 379 above
398	-	Same as claim 380 above
399	261	"fixing or immobilizing" step is found in specification (page 28; see especially Wahl, et al. U.S. Patent No. 4,302,204)
400	262	
401	263	
402	-	See specification (page 28; see especially Wahl et al., U.S. Patent No. 4,302,204)
403	-	<i>ibid</i>
404	-	<i>ibid</i>
405	261	Same as claim 399 above
406	262	
407	263	
408	-	Same as claim 402 above
409	-	<i>ibid</i>
410	-	<i>ibid</i>
411	275	"or hybridizing with" inserted for MBE first portion; "or segments" inserted for MBE second portion; & "more than one" SE substituted for a SE "or hybridizing with" inserted for SE nucleic acid portion
412	275	Complex formulation; & Other changes follow claim 411 above
413	275	Changes follow claim 411 above except that "more than one" MBE is recited
414	275	Changes follow claim 413 above
415	275	Complex formulation; & Other changes follow claim 414 above

416	275	Same as claim 411 above except for recitation of "one or more polynucleotides which have been chemically modified or artificially altered" for SGP
417	275	Complex formulation; & Same as claim 416 above
418	276	
419	276	
420	278	Support for "greater than 5" is in specification (page 22, first paragraph)
421	278	
422	277	Recitation for "greater than 1" is in specification (page 22, first paragraph)
423	277	Except that "one or more chemically modified or artificially altered polynucleotides" substituted for SGP
424	277	Support for "greater than 5" is in specification (page 22, first paragraph)
425	277	Except that "one or more chemically modified or artificially altered polynucleotides" substituted for SGP
426	279	Support for "greater than 1" is in specification (page 22, first paragraph)
427	279	Same as claim 426 above except that "one or more chemically modified or artificially altered polynucleotides" substituted for SGP
428	279	Support for "greater than 5" is in specification (page 22, first paragraph)
429	279	
430	279	Same as claim 428 above
431	279	Same as claim 429 above
432	-	Support is in specification (page 16, first paragraph; and page 22, first paragraph)
433	-	<i>ibid</i>
434	280	
435	280	
436	281	
437	282	See specification (page 28)

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It is respectfully submitted that the subject matter of new claims 283-437 is fully supported by the original disclosure. Their entry does not constitute the insertion of new matter, and is, therefore, earnestly urged.

* * * * *

<u>New Claim No.</u>	<u>Prior Related Claim</u>	<u>Changes in New Claim/Comments</u>
183	229	
184	228	
185	231	
186	232	"or an M13 phage variant" inserted for "or a variant thereof"
187	233	
188	234	
189	235	"sequence of repeating low complexity" inserted for "sequence of low complexity"
190	236	"sequence of repeating low complexity" inserted for "said sequence"
191	237	deletion of "non-radioactive"
192	238	"radioactive compound" inserted for "radioactive moiety"
193	239	
194	240	
195	241	
196	242	
197	243	
198	244	
199	245	insertion of "a radioactive measurement" as a Markush member
200	246	
201	247	no "universal" or "non-radioactive" recitation
202	248	no "universal" or "non-radioactive" recitation
203	249	
204	250	
205	251	

<u>New Claim No.</u>	<u>Prior Related Claim</u>	<u>Changes in New Claim/Comments</u>
206	252	
207	253	
208	254	
209	255	
210	256	
211	257	
212	258	
213	259	
214	260	
215	261	
216	262	
217	263	
218	264	
219	270	
220	267	
221	266	
222	268	
223	269	
224	270	
225	272	
226	271	
227	273	
228	274	"or an M13 phage variant" inserted for "or a variant thereof"
229	275	"sequence of repeating low complexity" inserted for "sequence of low complexity"
230	276	"sequence of repeating low complexity" inserted for "said sequence"
231	277	
232	280	
233	284	
234	281	

<u>New Claim No.</u>	<u>Prior Related Claim</u>	<u>Changes in New Claim/Comments</u>
235	283	
236	282	
237	285	
238	286	"or an M13 phage variant" inserted for "or a variant thereof"
239	287	
240	288	
241	289	"sequence of repeating low complexity" inserted for "sequence of low complexity"
242	290	"sequence of repeating low complexity" inserted for "said sequence"
243	291	no "non-radioactive" recitation
244	292	"radioactive compound" inserted for "radioactive moiety"
245	293	
246	294	
247	295	no "non-radioactive" recitation
248	296	
249	297	
250	298	
251	299	no "non-radioactive" recitation insertion of "a radioactive measurement" as a Markush member
252	300	
253	301	no "universal" or "non-radioactive" recitation "more than one signal generating portion" "inserted for "more than one signalling entity"
254	303	no "non-radioactive" recitation
255	306	
256	306	

<u>New Claim No.</u>	<u>Prior Related Claim</u>	<u>Changes in New Claim/Comments</u>
257	307	no "universal" or non-radioactive recitation "more than one signal generating portion" inserted for "more than one signalling entity"
258	237 (SERIAL NO. 08/032,769)	
259	310	no "universal" or "non-radioactive" recitation
260	311	
<u>METHOD OR KIT</u>	<u>SERIAL NO 08/032,769</u>	
261	154, 211, 217, 223	dependent from composition claims.
262	155	
263	156	
264	199	no "non-radioactive" recitation
265	200	reference to detecting step in method "radioactive compound" inserted for "radioactive moiety"
266	201	
267	202	
268	203	reference to detecting in method no "non-radioactive" recitation
269	204	reference to detecting step in method
270	205	reference to detecting step in method
271	206	reference to detecting step in method
272	207	no "non-radioactive" recitation insertion of "a radioactive measurement" a Markush member
273	208	insertion of "the analyte" for "the universal signalling entity"
274	229	no "universal" or "non-radioactive" recitation
275	209, 214, 220 & 224	no "universal" or "non-radioactive" recitation

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<u>New Claim No.</u>	<u>Prior Related Claim</u>	<u>Changes in New Claim/Comments</u>
276	210	no "non-radioactive" recitation
277	216	
278	219	
279	216 & 219	
280	225	no "universal" or "non-radioactive" recitation
281	157 (a method)	
282	228	insertion of "the molecular bridging entity" for "at least one component of said detectable complex"

Before addressing the issues in the two previous office actions, Applicants wish to inform the Examiner that the grant of European Patent No. 0 128 332 B1 was published by the European Patent Office on August 2, 1995. This patent is based upon the priority document, U.S. Patent Application Serial No. 06/491,929, filed originally on May 5, 1983. A copy of EP 0 128 332 B1 is attached to this Preliminary Amendment as Exhibit 1.

I. ISSUES FROM MAY 19, 1995 OFFICE ACTION (SERIAL NO. 08/342,667)

A. Entry of After Final Amendments Filed 5/31/94 & 6/16/94

In the May 19, 1995 Office Action issued in the predecessor application (Serial No. 08/342,667), the Examiner indicated that the after final amendments filed 5/31/94 and 6/16/94 were not entered because their entry was not requested in the file-wrapper continuation request. Accordingly and as indicated above in the opening remarks, Applicants have requested entry of the amendments from their aforementioned May 31, 1994 Amendment Under 37 C.F.R. §1.116 as they relate to the specification. These amendments affect pages 2, 3, 44 and 50 in the specification.

B. Provisional Election of Species

Applicants and their attorney acknowledge the indication that the previous provisional species election in the predecessor's parent application (Serial No. 07/805,274) was made without traverse. A similar species election was made in the sister (Serial No. 08/032,769). With respect to the instant application, Applicants would like to confirm their previous provisional elections from their two previous applications, but with traverse, as elaborated below.

At the outset, Applicants note that the instant invention is now directed to a composition, method and kit useful for detecting an analyte having a molecularly recognizable portion thereon. The claims include a signal generating portion providing for a detectable non-radioactive signal, or a signalling chemical moiety which provides a detectable signal. It is submitted that the claimed subject matter is novel, useful and unobvious, and together with the members for the analyte and molecular bridging entity first portion, all of which are fully disclosed and claimed in the instant application, form a single general inventive concept which should properly be examined in the same application. Furthermore, the members for the analyte and bridging entity first portion represent a reasonable number of species having characteristics in common, such that the generic subject matter for the members - and not single individual species - should be the focus of examination in the same application. Particular embodiments for the analyte and bridging entity first portion are set forth in dependent composition claims 152-171 and 214-233.¹

¹ It should not be overlooked that the instant claims emerged into their present form, largely as a result of "recasting" the then-pending composition claims in Serial No. 07/805,274 in response to a rejection for improper Markush groups under 35 U.S.C. § 112, second paragraph. See the October 13, 1992 Office Action issued in Serial No. 07/805,274 and the subsequent December 22, 1992 Amendment Under 37 C.F.R. § 1.115. Although not subject to a rejection, the corresponding method claims were similarly recast to conform with the composition claims. See the March 16, 1993 Preliminary Amendment Accompanying Request for a Continuation Application Under 37 C.F.R. § 1.60 submitted in Serial No. 08/032,769 (filed on March 16, 1993).

If the species recited in the generic claims are allowed, then it follows that the other species in the aforementioned dependent claims will also be found allowable as part of the generic claims. Applicants respectfully submit that they are entitled to claim their invention as broadly as the prior art permits, commensurate with the disclosure requirements of 35 U.S.C. § 112. Under such a well-established legal principle, Applicants are entitled to claim and to pursue the full breadth of their generically disclosed invention in the same application. Applicants respectfully request, therefore, that the Examiner reconsider and withdraw the species election, and examine all of the instant claims.

C. The Rejection Under 35 U.S.C. § 112, Second Paragraph

In the May 19, 1995 Office Action, claims 194, 199, 200, 209-248, 253, 254 and 263-311 were rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. On pages 2-4 of the Office Action, the Examiner stated:

[1]The claims 194, 199, 200, 209-248, 253, 254 and 263-311 are vague and indefinite because there is no recited cooperativity between the first portion and the second portion of the molecular bridging entity of claim 194, for example. Are they covalently linked? Are they ionically linked? Are they not linked at all?

[2]Claims 194 etc. cite the direct versus indirect detectability of a signal corresponding to signal detection as first given in the claims in claim 194, line 10. No distinguishing definitions of direct versus indirect is present in the disclosure as filed. What are the metes and bounds of these limitations? It is noted that a simple interpretation of direct may be that radioactive labels are meant, however, this conflicts with the "non-radioactive" signal generating moieties of the specification, for example. Even this interpretation is confusing in that biotin labeled signalling entity may be detected by radioactive labeled antibody. Is this a direct signalling or does the antibody binding make it indirect? For example, a dye molecule must have a light source for detection via reflected or absorbed light. This appears to be most reasonably interpreted as inclusive of indirect detectability. In summary, the direct versus indirect detection of signals is undefined regarding metes and bounds. Clarification is requested.

[3]What are the metes and bounds of the "low" in low complexity in claims 221 and 235? No definition has been disclosed regarding these terms which also cause concern as noted in the below summarized art rejection. Clarification is requested.

[4]What are the metes and bounds of the phrase "variant thereof" given in the last line of claims 232 etc? Without some definition of the scope of this phrase it could mean anything leading to an indefinite scope for these claims. Clarification is requested.

[5]What is meant by the metes and bounds of the citation of "modified" in claims 227, 234, etc? Clarification is requested as to the desired scope of the claims.

The indefiniteness rejection is respectfully traversed.

In order to ensure that each and every issue under §112, second paragraph, is thoroughly addressed, Applicants' attorney has taken the liberty of inserting bold bracketed numbers before each issue. The comments which follow below are directed to these bold designations.

[1] Regarding the issue of cooperativity between the first and second portions of the molecular bridging entity, it is respectfully submitted that this matter is well addressed in the disclosure as filed. With the specification in hand, a person skilled in the art would readily understand the relationship between these two elements as set forth in the instant claims. For example, in the section titled "PROCESSES OF PREPARATION" (beginning on page 22, last four lines, and continuing through the first paragraph on page 27), Applicants provide ample description of both first and second portions and their preparation as a molecular bridging and signalling entities in accordance with the instant invention. See in particular, page 23, second paragraph, through page 24, first paragraph, and the several publications listed therein. Furthermore, in Example 32 (page 57, last paragraph, through page 61, item no. 15), Applicants provide a detailed protocol and procedure for preparing and using the instantly claimed bridging entity for detection. The cooperativity between the molecular bridging entity first and second portions would be apparent to the skilled artisan from the instant claims when read in light of the specification and drawings. Applicants point out that if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, USPQ 81, 94 (Fed. Cir. 1986). Furthermore, it is well established that "the law does not require all of the claims to recite each and every element necessary to the operation of the invention. . . . Were this not the case, the claims would be prolix to the point of obscuring the inventive concept to which the claims are directed. It is the function of the specification, not the claims, to set forth sufficient detailed information to enable one skilled in the art to make or use the invention." General Electric Co. v. United States, 206 USPQ 260, 283-84 (Ct. Cl.

Cl. Trial Div. 1979), *aff'd on other grounds*, 654 F.2d 55, 211 USPQ 867 (Ct. Cl. 1981). Moreover, to require that the instant claims be restricted to a specific cooperative embodiment between the elements at hand would actually invite others - contrary to the general purpose and intent of the patent system - to appropriate the instant invention without infringing the claims, thereby depriving Applicants of their rightfully claimed invention.

[2] With respect to the issue of direct versus indirect signal detectability, Applicants reiterate that this language is absent in all of the independent claims (150, 201, 202, 253, 255, 257, 259, 274 and 275), and is only maintained in specific dependent claims (191-198, 243-250 and 264-271). Having relegated this language to the dependent claims, Applicants believe that the meaning of the direct and indirect terminology has been clarified both with respect to the independent claims and the dependent claims. The person skilled in the art would easily understand such meaning from reading each of the dependent claims containing the direct or indirect language in conjunction with the instant disclosure and the state of the art at the time this invention was made. Acknowledgement is made of the several questions posed by the Examiner on page 3 of the May 19, 1995 Office Action. In light of the new claims above, however, Applicants are hopeful that a specific answer to each question is not necessary.

[3] With respect to the phrase "low complexity" in claims 221 and 235, Applicants reiterate that new dependent claims (177-178, 189-190, 229-230 and 241-242) call for "a nucleic acid sequence of repeating low complexity." The new language is actually taken from the originally filed claims in the seminal application. See, for example, original claims 78, 90, 113, and 131. It is respectfully submitted that the use of terms like "low" does not render a patent claim indefinite unless a person of ordinary skill in the art would not be able to determine from the claims what would be infringing and what would not be infringing. Any vagueness created by the use of non-numerical terms can be cured by the character of the invention. In the situation at hand, the skilled artisan would readily appreciate in reading the specification, that the repeating low complexity recitation in the claims clearly refers to the repetitive nature of the instant nucleic acid sequence. See, for example, ZMI Corp. v. Cardiac Resuscitator Corp., 2 USPQ 1985, 1989 (D. Ore. 1987), *rev'd in*

part, vacated in part and remanded, 844 F.2d 1576, 6 USPQ 1557 (Fed. Cir. 1988).

[4] Concerning the phrase "variant thereof," Applicants point out that the language in the new dependent claims (176, 186 and 238) calls for Markush members including "an M13 phage, or an M13 phage variant." The new language is taken from originally filed claims 32, 45, 127 and 136, each of which recited "wherein said phage is M13 or a variant thereof." As now recited in the instant new claims, the term "variant" applies to the M13 phage. Even without the disclosure in hand, the skilled artisan would understand the meaning of this term to include M13 variants.

[5] Turning to the word "modified" as applied to "oligo- or polynucleotide" in the new claims above (167, 172, 182, 187-188, 219, 224, 234 and 239-240), Applicants note at the outset that modified nucleotides and polynucleotides containing such modified nucleotides are disclosed in U.S. Patent Nos. 5,328,824; 5,449,767; 5,476,928; 4,711,955; and 5,241,060, all of which have been incorporated by reference into the instant application. See page 20, last paragraph, through page 21, first paragraph of the instant specification. See also this Amendment, page 2, last paragraph, through page 3, first paragraph. Furthermore, in the specification (page 21, full paragraph), Applicants provide a discussion of other natural biologically modified polynucleotides which can be used in accordance with the instant invention. Applicants would respectfully like to point out that the term "modified" as applied to nucleic acids, oligonucleotides, polynucleotides, and the like, is both recognized and accepted in the art. A number of U.S. patents have issued over the years with claims having similar if not identical language to the language at issue here. These patents include but are not limited to the following six (6) patents:

<u>Exhibit</u>	<u>Patent No.</u>	<u>Inventor(s)</u>	<u>Recited Terminology/Claims</u>
2	5,270,184	Walker et al.	modified nucleotide (claims 1-14)
3	5,124,246	Urdea et al.	modified nucleotides (claim 9)
4	5,093,232	Urdea et al.	modified nucleotide (claims 1-14)

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5	4,987,065	Stavrianopoulos et al.	modified nucleic acid base (claims 1-3) modified base (claims 13-15, 20-21 & 23)
6	4,948,882	Ruth et al.	modified nucleoside monomer (claims 3-4)
7	4,835,263	Nguyen et al.	modified chain of nucleotides (claims 1 & 3-6)

A copy of each of the above-listed six (6) patents are attached hereto as Exhibits 2-7. It is respectfully submitted that the instant use of the expression "modified oligo- or polynucleotide" is altogether proper and appropriate under the law as evidenced by the issuance of a vast number of patents with similar phraseology. Applicants earnestly request that the instant usage be given similar deference as in the case of these other issued U.S. patents.

In light of the presentation of new claims 150-282 above, the foregoing arguments and submitted exhibits (2-7), it is respectfully submitted that all grounds of the indefiniteness rejection have been removed or overcome.

Commonality of Ownership

Pursuant to their obligations under 37 C.F.R. §1.56, Applicants wish to inform the Examiner and The Patent Office that all of the claims were commonly owned at the time the first application in the family was filed in 1983, and this commonality of ownership continues for the new claims (150-282) submitted above.

D. The Rejection Under 35 U.S.C. §103

In the May 19, 1995 Office Action, claims 194, 199, 200, 209-248, 253, 254 and 263-311 were rejected under 35 U.S.C. §103 as being unpatentable over Dunn et al. (1977) ["A Novel Method to Map Transcripts: Evidence for Homology between an Adenovirus MRNA and Discrete Multiple Regions of the Viral Genome," Cell 12:23-36 (1977)] taken in view of Ward et al. [U.S. Patent No. 4,711,955]. In the Office Action (pages 5-7), the Examiner stated:

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The instant invention is directed to compositions for detecting an analyte via the recognition and binding of a bridging entity to the analyte. The bridging entity contains two portions, one portion that recognizes and binds the analyte and a second portion containing a polynucleotide segment. The polynucleotide segment of the second portion of the bridging entity hybridizes to a signalling entity via a complementary nucleic acid segment in the signalling entity. The signalling entity may be non-radioactively labeled as to be detectable. The detection of the label indicates the presence of analyte. Kit-like compositions for the practice of the method are also claimed. The specific limitations of certain claims are discussed below as to how they are made obvious by the above combination of references.

Dunn et al. (1977) disclose a sandwich hybridization technique wherein an RNA construct containing two portions performs as a bridging entity as in the instant invention. The two portions of the RNA construct consist of an analyte recognition and binding portion and a tail as discussed on page 23, bridging paragraph between the first and second columns. The tail is a polynucleotide segment that hybridizes to a radiolabeled signalling entity for detection. The detection of the radiolabel is indicative of analyte detection. The methodology is depicted in Dunn et al. (1977) on page 24 in Figure 1 with detection results shown in Figure 2 etc. in the reference. This reference generically discloses the instant invention at said page 23 citation but lacks the use of a nonradioactively labeled signalling entity. Additionally, the generic scope of practice of the sandwich hybridization technique of Dunn et al. (1977) is suggested in that the page 23 summary of the technique is generic in nature and the system disclosed by Dunn et al. (1977) to illustrate the technique is stated as being a "model system" on page 23, second column, line 9. These disclosures clearly suggest a scope broader than that of detecting viral RNA map transcription sites as given in the experimental examples in the reference.

Ward et al. generically discloses the substitution of biotinylated nucleic acids as a non-radioactive label for radiolabeled nucleic acids in hybridization detection methods. The disclosure of Ward et al. includes several motivations for the substitution of non-radioactive labels such as based on biotin for radiolabels in columns 1-3 in the section entitled "BACKGROUND OF THE INVENTION" and also gives a reasonable expectation of success for this substitution via numerous examples therein.

On pages 6 and 7 of the Office Action, the Examiner concluded that

... it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the compositions composed of bridging and signalling entities using non-radioactive labels for detection as instantly claimed because Dunn et al. (1977) disclose bridging and signalling entities as instantly claimed with radiolabel mediated detection and Ward et al. disclose both the motivation and reasonable expectation of success for substituting nonradioactive labels such as biotin for radiolabel mediated detection during hybridization procedures resulting therefrom in the practice of the instantly claimed invention.

The obviousness rejection is respectfully traversed.

In response, Applicants respectfully point out that there are several significant reasons why the combination of cited documents would not have rendered the instant invention obvious to a person of ordinary skill in the art.

1. As the primary reference, Dunn et al. does not reach or even allude to the instant universal concept.

(a) Dunn's "tail" is the analyte.

Dunn et al. disclose a method for mapping transcripts using a so-called "two-step hybridization procedure (sandwich hybridization)." The subject sequence in Dunn's paper is an Ad2-SV40 hybrid virus (called "Ad2 + ND1") that occurs naturally in infected cells. The Ad2 + ND1 hybrid sequence was originally isolated by Lewis et al. (1969). See Dunn et al., page 23, right column, first full paragraph. See also Lewis et al., "A Nondefective (Competent) Adenovirus-SV40 Hybrid Isolated From The AD.2-SV40 Hybrid Population, copy attached hereto as Exhibit 8. There was absolutely no disclosure in Dunn et al. relating to the instantly claimed invention including the analyte-specific molecular bridging entity that also comprises a nucleic acid portion capable of hybridizing to a nucleic acid portion in a signalling entity. Furthermore, the "RNA tails" referred to in several instances in Dunn's paper are natural SV40 RNA sequences which are part of the naturally occurring hybrid virus, i.e., part of the target (analyte). Dunn's "analyte" is no more than a natural adenovirus-simian nucleic acid hybrid. As such, Dunn's "RNA tails" are the target analyte, and they do not represent in any sense sequences or portions specifically chosen or engineered in accordance with the instant "universal" invention or concept.² In all respects, the Dunn paper does not reach or relate (narrowly or

²The "universal" nature of the instant invention was well-described in four pages in Applicants' September 8, 1994 Amendment Under 37 C.F.R. §1.116 (see page 7, third paragraph under item [1], continuing through the first paragraph on page 11). Briefly, at least two significant and different "universal" aspects are provided by the instant invention. One "universal" aspect concerns the "universal" array of analytes which can be detected using the instant invention. The other "universal" aspect involves the capability of using the signalling entity with any number of analyte-specific probes (otherwise called the "molecular bridging entity" in the instant claims).

broadly) to the instant invention. After describing in the paper's first paragraph "several [previous] approaches to mapping the regions of adenovirus type 2 (Ad2) DNA," Dunn et al. describe their own efforts in the second paragraph:

We have developed a technique (sandwich hybridization) in which RNA is hybridized to defined fragments of viral DNA bound to nitrocellulose filters such that the 3' or 5' end of the RNA protrudes as a single-stranded tail. The DNA sequences complementary to the "tail" sequences can be determined by a second round of hybridization using specific fragments of viral DNA labeled with ³²P. **By using DNA radioactively labeled to high specific activity in vitro as a probe**, we have overcome some of the limitations to mapping RNA labeled in vivo.
[bold and underline added]

Dunn's labelled probe is, therefore, the analyte-specific moiety with a radioactive signal, in other words, a conventional radioactive labelled probe. In sharp contrast to Dunn et al., the instant invention provides a unique composition comprising a molecular bridging entity and signalling entity which is novel, universal, diverse and altogether different. Only the instant molecular bridging entity could be construed as corresponding, however remotely, to Dunn's conventional probe in that the former comprises a portion specific to the analyte. And there, the resemblance ends.

It is at this juncture in their paper that Dunn et al. state that "[a]s a model system, we have used RNA from cells productively infected with an Ad2-SV40 hybrid virus . . ." Therefore, whatever "model" system contemplated by Dunn et al. is clearly confined to overcoming some of the so-called "limitations to mapping RNA labeled in vivo." Accordingly, the assertion that Dunn's "disclosures clearly suggest a scope broader than that of detecting viral RNA map transcription sites as given in the experimental examples in the reference" is without merit or basis.

(b) Dunn's paper is limited to transcript mapping and the use of sandwich hybridization a la Ranki.

Dunn's disclosure is directed to the mapping of adenovirus type 2 RNA transcripts. In fact, in their opening lines under the "Summary," Dunn et al. assert

that "[a] method has been devised which permits mapping of transcripts by a two step hybridization procedure (sandwich hybridization)."

As explained above, Dunn's "tail" sequences are part of the analyte, and do relate at all to a molecular bridging entity, as set forth in the instant claims. It is unfathomable how the same molecule or entity could serve simultaneously as analyte and analyte-specific moiety. It has already been established previously that Dunn's procedure uses a ^{32}P DNA probe.

[It should not be overlooked that previous claims in three predecessor applications [Serial No. 07/607,787; 07/805,274 and 08/032,769; filed on October 26, 1990, December 10, 1991 and March 16, 1993, respectively] were rejected over the Ranki disclosure, U.S. Patent No. 4,486,539 (issued on December 4, 1984), previously cited of record. The rejection over Ranki et al. was withdrawn in the two most recent office actions dated May 19, 1995 and August 23, 1994 which were issued in Serial Numbers 08/342,667 and 08/032,769. It is respectfully submitted that as a cited document, Dunn et al. is no better than Ranki et al. Both are directed to sandwich hybridization techniques in which an immobilized capture probe and signalling probe hybridize to separate target nucleic acid analyte sequences. In view of the fact that the previous art rejection based upon the Ranki patent has been withdrawn, any art rejection based upon Dunn's paper is substantially similar, and should likewise be withdrawn or withheld in the examination of the latest claims.]

2. Other secondary considerations point to the nonobviousness of the instant invention.

Under the *Graham v. John Deere* test for nonobviousness, a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made involves factual findings with respect to (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) where relevant, objective evidence of nonobviousness, e.g., long-felt need in the art, commercial success, failure of others, copying, and unexpected results (the so-called "secondary considerations"). As explained by Kenneth J. Burchfiel in his recently

published book, Biotechnology and the Federal Circuit, (The Bureau of National Affairs (BNA), Washington, D.C., 1995, pages 80-81):

The Federal Circuit has placed increasing emphasis and reliance on "secondary considerations" or "objective evidence,"¹⁴ making it clear that contrary to the statement of the Supreme Court,¹⁵ such evidence is not secondary,¹⁶ but is always relevant and must be considered in determining obviousness;¹⁷ indeed, it "may often be the most probative and cogent evidence in the record."¹⁸ The primacy of secondary considerations over purely technical factors, such as the scope and content of the prior art, has become increasingly evident from the obviousness decisions of the Federal Circuit.¹⁹ [citations omitted]

Secondary considerations in the form of unexpected results and advantages have already been submitted in prior applications in the form of separate declarations by Drs. Christine L. Brakel and Dean L. Engelhardt. It should be noted that none of the results or advantages described in the Brakel or Engelhardt Declarations are disclosed or even alluded to in the cited Dunn and Ward documents.

It should also be noted that an entire product line called BioBridge® (since then renamed as OligoBridge™) has been developed and marketed by the instant assignee, Enzo Diagnostics, Inc. Although submitted previously in the prosecution, copies of BioBridge® product literature are attached as Exhibit 9 for the convenience of the Examiner. Also attached as Exhibit 10 are pages 37 and 38 from Dr. Robert H. Symons' 1989 book titled Nucleic Acid Probes [CRC Press, Boca Raton, Florida, Chapter 2 "Preparation and Detection of Nonradioactive Nucleic Acid and Oligonucleotide Probes," J. L. McInnes and R. H. Symons].

Finally, Applicants are also submitting a copy of an abstract coauthored by Drs. Brakel and Engelhardt and presented at the 75th Annual Meeting of the American Society of Biological Chemists and the 68th Annual Meeting of The American Association of Immunologists held June 3-7, 1984 in St. Louis, Missouri. A copy of this abstract titled "Non Radioactive Biotin - Dependent Hybridization/ Detection Using Unlabeled Probe DNA," is attached as Exhibit 11. The abstract (Exhibit 11) is related to the instant invention and it discloses that the method described therein "was found to be greater than the sensitivity obtained using directly biotinylated probes, prepared either by nick translation or terminal labeling."

That information comports with the results set forth in Dr. Brakel's Declaration Under 37 C.F.R. §1.132.

The Examiner is respectfully urged to take into account any or all of the above submitted information in reconsidering the obviousness rejection.

II. ISSUES IN JANUARY 10, 1995 OFF. ACTION (SER. No. 08/032,769)

A. Withdrawal of Objections/Rejections Not Reiterated

Applicants acknowledge with appreciation the indication that the rejections and/or objections not reiterated from the previous August 23, 1994 Office Action have been withdrawn. Applicants also appreciate that the finality of that Office Action has been withdrawn.

B. The First Objection and Rejection Under 35 U.S.C. §112, First Paragraph

The specification stands objected to for failing to provide support for the invention as now claims and claim 156 was rejected for new matter, both under 35 U.S.C. §112, first paragraph. In the Office Action (pages 2-4), the Examiner stated:

The NEW MATTER rejection of claim 156 is reiterated and maintained as set forth in the final rejection office action mailed 8/23/94. Consideration of the arguments, filed 9/8/94, results in noting that the citation pointed to by applicants at page 61, procedure no. 15, to support present claim 156 discloses a hybridization practice, which is deemed the practice of forming complexes, as occurring concomitantly and not sequentially between the bridging entity and both the signalling entity and the target. The determinative line is "allowed to hybridize to target DNAs and to each other". Nothing in the cited phrase indicates a sequential nature to the complex formation as is presently given in claim 156. Even if applicants wish to argue that the order of wording in the above cited phrase is significant, it is noted that hybridization to the target is given first before the phrase "to each other" again lacking support for the reverse practice as given in claim 156. Additionally, the word "mixed" is present in the first line of said procedure no. 15 but this "mixed" word is not accompanied by a disclosure that hybridization occurs during the mixing. It was well

known in the art at the time of the instant invention that hybridization requires appropriate conditions that are more limited and defined than simply mixing nucleic acids together. Thus, the mixing practice is not deemed to support hybridization between bridging and signalling entities prior to contact with target nucleic acid. Therefore, as stated previously, claim 156 lacks written support in the disclosure as filed. It is lastly noted that a similar rejection of claim 155 has been withdrawn because the cited support for this claim is deemed persuasive.

The objection for lack of support and the new matter rejection are respectfully traversed.

Applicants acknowledge, even with appreciation, the detailed analysis given by the Examiner in the above-quoted portion. Notwithstanding its details, however, the analysis simply overlooks several tenets expostulated by the courts in setting up and applying the legal standards for adequate description and new matter.

First, the legal test for determining compliance with the written description requirement is whether the disclosure of an application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter. See Ex parte Rohrer, 20 USPQ2d 1460 (Bd. Pat. App. & Int'f 1991); Ex parte Holt, 19 USPQ2d 1211, 1213 (Bd. Pat. App. & Int'f 1991); and Ex parte Remark, 15 USPQ2d 1498, 1506 (Bd. Pat. App. & Int'f 1990).

Second, it is not necessary that the claimed subject matter be described identically, but the disclosure originally filed must convey to those skilled in the art that the applicant invented the subject matter later claimed. Rohm & Haas Co. v. Mobil Oil Corp., 212 USPQ 354 (D. Del. 1981) (citing Treatise); Ex parte Rodgers, 27 USPQ2d 1738, 1743 n.11 (Bd. Pat. App. & Int'f 1992). It is not necessary that the claimed subject matter be described in *ipsis verbis* to satisfy the written description requirement of 35 U.S.C. §112. Nelson v. Bowler, 1 USPQ2d 2076, 2078 (Bd. Pat. App. & Int'f 1986).

Third, it is not necessary for the applicant to reveal a conscious appreciation on the part of the applicants of the significance of the limitation in question. . . The written description requirement can be satisfied by showing that the disclosed

subject matter, when given its 'necessary and only reasonable construction,' inherently (i.e., necessarily) satisfies the limitation in question. Behr v. Talbott, 27 USPQ2d 1401, 1407 (Bd. Pat. App. & Int'f 1992).

Fourth and finally, the basic test of whether the prior disclosure reasonably conveys to those skilled in the art that the applicant had possession of the later claimed subject matter at the time of the earlier disclosure requires specific reference to the knowledge of those skilled in the relevant art [in this instance, the biotechnology arts]. Vas-Cath, Inc. v. Mahurkar, 935 F-2d 1555, 1566, 19 USPQ2d 1111, 1116 (Fed. Cir.1991).

In the case of new claim 263 (formerly claim 156), Applicants are claiming a variation in the detection method characterized in that the forming step comprises contacting said bridging entity with the signalling entity to form a first complex and thereafter contacting the first complex with the analyte to form the detectable complex. Applicants respectfully maintain that the cited portions (procedure no. 15) reasonably convey to the skilled artisan that Applicants were in possession of the instant subject matter of claim 156 (now new claim 263) at the time of the original application was filed in 1983. The fact of the matter is, the phrase "allowed to hybridize to target DNAs and to each other" is reasonably construed as indicating that the molecular bridging entity and signalling entity are allowed to hybridize to each other in advance of hybridization to target DNAs. Surely, the absence of a comma, or the substitution of a different conjunction ("and" instead of "or"), or even the mere change in word order of two elements in a sentence should not be dispositive on this issue, particularly when the courts have clearly indicated otherwise (identical or *ipsis verbis* description not necessary to satisfy the written description requirement. Rohm & Haas, Rodgers & Nelson cases, *supra*).

Moreover, the assertions that "[i]t was well known in the art at the time of the instant invention that hybridization requires appropriate conditions that are more limited and defined than simply mixing nucleic acids together" and that "the mixing practice is not deemed to support hybridization between bridging and signalling entities prior to contact with target nucleic acid" flies against the thrust of the law. Such assertions would minimize the knowledge of those skilled in the biotechnology arts which should properly be considered in evaluating the subject matter in new

claim 263. (specific reference to the knowledge of those skilled in the biotechnology arts is required. Vas-Cath, Inc. v. Mahurkar, supra). Mixing is often taken in the art as a step indicative of a process leading to hybridization, admittedly requiring hybridizable conditions. Surely, it was well within the ambit of skill and knowledge of the ordinary artisan that "mixing" of two complementary nucleic acid sequences (as set forth in the cited protocol) typically produces hybridized duplexes, except in those instances, of course, where the conditions are highly caustic or so extremely stringent that hybridization is effectively prevented.

Reconsideration of the new matter rejection is respectfully requested in light of the legal standards set forth above. It is believed that if consideration is given to these standards, then the proper and reasonable interpretation of procedure no. 15 (page 61) will result in a finding of support for new claim 263. Denying the benefit of this subject matter could only be the consequence of applying a stricter "identical or *ipsis verbis*" written description requirement, than any heretofore enunciated by the courts. That the courts have been loathe to apply such a strict standard should be carefully considered.

C. The Second Objection & Rejection Under 35 U.S.C. §112, First Paragraph

Claims 154-163, 171-208, 211-213, 217-219, 223, 227, 229, and 233-238 stand rejected under 35 U.S.C. §112, first paragraph, as the disclosure is enabling only for claims limited to methods including at least one washing step to separate signal-generating portions corresponding to analyte detection from such portions not in a complex with analyte via a bridging entity. In the Office Action (page 4), the Examiner noted:

... that such a minimal washing is discussed on page 28, first full paragraph, which summarizes the invention. No guidance is supplied anywhere in the specification for performing the claimed method without at least one washing step. Without some guidance the claims are deemed broader in scope than the specification enables leaving undue experimentation for any other practice lacking said washing. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The objection and rejection for limited enablement are respectfully traversed.

At the outset, Applicants draw attention to the disclosure on page 28 in the specification in which washing is described. The disclosure provides:

The composition suspected of containing the analyte is incubated with the bridging entity for a time and under conditions sufficient to allow complexation between the recognizable portion on the bridging entity. These conditions will vary depending on the nature and amount of the analyte and of the bridging entity. Normally, after complexation has occurred, the sample is washed with neutral solution to remove excess bridging entity. Alternatively, no wash is carried out at this stage but signalling entity is added to the mixture and a wash is carried out after annealing has occurred between the polynucleotide strands on the bridging entity and on the signalling entity respectively. Hybridization of the bridging entity strand to the signalling entity strand is carried out under hybridizing conditions and under any set of stringency conditions. A final wash may be necessary prior to generation of signal.

It is quite plain from reading the above-quoted portion that washing may be a suggested, even a preferable step in carrying out the instantly claimed method, but it is by no means necessary to satisfy the enablement requirements of 35 U.S.C. §112, first paragraph. The suggestive or preferred nature of washing steps vis-a-vis the instant method is buttressed by several modifiers or limitations in the portion quoted above. **Normally**, after complexation has occurred, the sample is **washed**. **Alternatively, no wash** is carried out at this stage but signalling entity is added to the mixture and a **wash** is carried out after annealing. **A final wash may be necessary** prior to generation of signal. All of these modifiers or limitations would reasonably lead the skilled artisan to believe that washing is not required, but could be preferably carried out in the instant method.

Furthermore, Applicants respectfully contend that guidance for performing the claimed method without at least one washing step is provided, in fact, by the above-quoted disclosure which logically indicates that washing is not required. Moreover, the knowledge of the skilled artisan should be taken into consideration in evaluating the instant disclosure for enablement under 35 U.S.C. §112, first paragraph. Surely, the skilled artisan would have been able to practice the instant method without a washing step based upon a reading of the disclosure and the skill that he or she already possessed.

Lastly, it should not be overlooked that the originally filed method claims, 1-71, were devoid of any washing step or embodiment. To that extent at least, washing steps were not contemplated at the time of the original filing as an indispensable feature or element of the instantly claimed method, but only as a suggested or preferred aspect.

In light of the remarks above, it is believed that the washing issue has been addressed and rendered moot.

D. The Third Objection and Rejection Under 35 U.S.C. §112, First Paragraph

Claims 175, 179, and 190 are rejected under 35 U.S.C. §112, first paragraph, as the disclosure is enabling only for claims limited to bridging entities that are completely circular thus containing both the first and second portions as exemplified in Figure 2 or alternatively completely linear. In the Office Action (pages 4-5), the Examiner stated:

[c]laims 175 etc. contain limitations where the first or alternatively the second portion are limited to being circular without limitation on the form of the second or first portions, respectively. This results in a scope that includes a circular first portion and a linear second portion, for example. In order to practice such an embodiment, a link between the linear portion and the circular portion is required. No such link has been instantly enabled. It would require a three bonding nucleotide residue. No such residue is instantly discussed thus leaving the practice of such a residue as an invitation to experiment which is deemed undue experimentation. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The above objection and rejection for limited enablement are respectfully traversed.

Applicants are willing to recognize that the embodiment cited by the Examiner may require a refinement in the chemistry to join the first and second portions of the molecular bridging entity. Such a refinement, which could even take the form of a branch, would be well within the ambit of skill of the artisan who would have the benefit of the instant disclosure as well as the knowledge in the art. Moreover, such an embodiment - and the issue of former claim 175 is but a single embodiment of the instant invention - would have been enabled without undue experimentation. It is noteworthy that in the section titled "PROCESSES OF PREPARATION," Applicants

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devote no less than five (5) pages of disclosure to attaching polynucleotides to other moieties, including other polynucleotide moieties. Attachment to the latter is described on page 25, second full paragraph, through page 26, first paragraph. Accordingly, it is respectfully submitted that the subject matter of former claim 175 (now embraced by composition claims 169, 174, 184, 221, 226 and 236) is fully enabled by the instant disclosure.

E. The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 154-163, 171-225, 227-229, 231 and 233-238 stand rejected for indefiniteness under 35 U.S.C. §112, second paragraph. In the Office Action (pages 5-7), the Examiner stated:

[1]Claim 154 etc. cite the direct versus indirect detectability of a signal corresponding to analyte detection as first given in the claims in claim 154, line 8. No distinguishing definitions of direct versus indirect is present in the disclosure as filed. What are the metes and bounds of these limitations? It is noted that a simple interpretation of direct may be that radioactive labels are meant, however, this conflicts with the "non-radioactive" of line 8 of claim 154, for example. Even this interpretation is confusing in that biotin labeled signalling entity may be detected by radioactive labeled antibody. Is this a direct signalling or does the antibody binding make it indirect? Claim 211, for example, cites a non-radioactive signal generating portion and then cites both direct and indirect detectability of a signal. This is confusing as to how to directly detect a non-radioactive signal. For example, a dye molecule must have a light source for detection via reflected or absorbed light. This appears to be most reasonably interpreted as inclusive of indirect detectability. In summary, the direct versus indirect detection of signals is undefined regarding metes and bounds. Clarification is requested.

[2]What are the metes and bounds of the "low" in "low molecular weight" in claim 163 and the "low" in "low complexity" of claims 183 and 197? No definition has been disclosed regarding these terms which also cause concern as noted in the below summarized art rejection. Clarification is requested.

[3]What are the metes and bounds of the phrase "variant thereof" given in the last line of claims 182 and 194? Without some definition of the scope of this phrase it could mean anything leading to an infinite scope for these claims. Clarification is requested.

[4]What is meant by the citation of "modified" and "naturally occurring" both in claim 195? How can a "modified" polynucleotide be "naturally occurring" or alternatively be still "naturally occurring" if it is "modified"? Do applicants wish the scope of the claims to include polynucleotides that are naturally modified? Clarification is requested as to the desired scope of claim 195.